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10/551,395	09/29/2005	Noelle Callizot	1386/22	3252

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,395	CALLIZOT ET AL.	
	Examiner	Art Unit	
	LESLIE A. ROYDS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-18* is/are rejected.

7)☒ Claim(s) *17 and 18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05 Dec 05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 13-18 are presented for examination.

Acknowledgement is made of the present application as a proper National Stage (371) entry of PCT Application No. PCT/EP04/05183, filed April 23, 2004, which claims benefit under 35 U.S.C. 119(a-d) to EPO Application No. 03291024.2, filed April 25, 2003, of which a certified copy was filed in the instant application September 29, 2005.

Applicant's Information Disclosure Statement (IDS) filed December 5, 2005 (two pages total) has been received and entered into the present application. As reflected by the attached, completed copy of form PTO-1449, the Examiner has considered the cited references.

Requirement for Restriction/Election

Applicant's election **with traverse** of flufenazine as the single disclosed specie of compound of formula (I) (i.e., wherein A represents a straight chain of 3 carbon atoms, R1 represents perfluoroalkyl of one carbon atom, R2-R5 each represent hydrogen, and R6 represents CH_2CH_2OR7, where R7 represents hydrogen), to which examination on the merits will be restricted, as stated in the reply filed May 8, 2009, is acknowledged by the Examiner.

Applicant traverses the requirement on the grounds that the cited reference of U.S. Patent No. 3,194,733 contains no teaching or suggestion of neuroprotective and/or neurotrophic effects on the central nervous system or the peripheral nervous system as set forth at p.1, l.6-11 of the instant specification or a suggestion of using such compounds for the treatment of amyotrophic lateral sclerosis, but rather teaches the compounds as tranquilizing agents. Applicant submits that the instant specification acknowledges that the claimed compounds are known and asserts that the special technical feature is the activity of the compounds, which is not taught or suggested in the cited '733 patent.

Applicant's traversal has been fully and carefully considered and is persuasive insofar as the

previous rationale for requiring an election of a single disclosed specie of compound of formula (I) was incomplete. For clarity of the record, the requirement is herein modified to properly set forth the reasons for requiring the election:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are compounds of formula (I) as set forth in instant claim 13.

The following claims are generic to these species: claims 13-14 and 16-18.

Applicant is required to elect a **single disclosed specie** of compound of formula (I) from those specifically claimed in instant claim 13.

Applicant is also notified that, ***in order for the reply to be considered compliant with the instructions set forth herein,*** the identity of each substituent (e.g., R1, R2, R3, R4, etc.) within the elected single disclosed specie **MUST** be provided, as well as a structural depiction of the single disclosed specie. Failure to provide each of these components will render the reply non-compliant.

Applicant is cautioned that the election of a particular specie of compound of formula (I), wherein the elected specie(s) is/are not adequately supported by the accompanying specification, may raise an issue of new matter under the written description requirement of 35 U.S.C. 112, first paragraph.

The species of compounds of formula (I) listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: Applicant's attention is directed to Ullyot (see U.S. Patent No. 3,058,979; 1962) to show that compounds of the instantly claimed structure were known in the prior art (see, specifically, col.1, l.25-col.2, l.21, which discloses a core structure identical to that instantly claimed, wherein R1 is, *inter alia*, perfluoroalkyl of 1-3 carbon atoms; A is a straight alkylene chain of 2-6 carbon atoms; R2, R3, R4 and R5 are each, *inter alia*, hydrogen; R6 is, *inter alia*, hydrogen, alkyl, etc.)

and that such compounds have utility in the treatment of mental disturbances, such as anxiety (col.1, l.14-20). Still further, Pongratz ("Treatment of Psychiatric Symptoms in Amyotrophic Lateral Sclerosis", *European Neuropsychopharmacology*, 2000; 10(Suppl.3):S116-117) is cited for its teaching that amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that affects both central and peripheral motor neurons (col.2, para.1, p.S116) and that the most important additional clinical features in advanced stages of ALS are, *inter alia*, psychiatric disturbances, such as anxiety and depression, and further teaches that anxiety in endstage ALS occurs is 32% of patients (col.2, Table 1, p.S116). As a result, in view of the facts that (1) Ullyot teaches that the disclosed compounds have efficacy in treating patients suffering from anxiety and (2) Pongratz teaches that a significant portion (i.e., at least 32%) of patients suffering from amyotrophic lateral sclerosis suffer from concomitant anxiety, it is clear that the compounds disclosed by Ullyot would also have efficacy in treating patients suffering from amyotrophic lateral sclerosis via the treatment of anxiety in said patients. Accordingly, this alleged special technical feature of the presently claimed invention (i.e., that the claimed compounds are effective for treating amyotrophic lateral sclerosis) cannot be the unifying feature of the presently claimed subject matter because it fails to demonstrate a contribution over what was already known in the prior art at the time of the invention.

Applicant is required, in reply to this action, to elect species consistent with the above instructions to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, Applicant

must indicate which are readable upon the elected species. See MPEP § 809.02(a).

The election of species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 C.F.R. 1.144.

Should Applicant traverse on the ground that the species are not patentably distinct, Applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the Examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Therefore, for the reasons *supra*, the requirement for restriction/election is proper. However, in view of the new reasoning set forth above, the requirement for restriction/election will not be made final at the present time.

As states *supra*, Applicant has elected, **with traverse**, flufenazine as the single disclosed specie of compound of formula (I) (i.e., wherein A represents a straight chain of 3 carbon atoms, R1 represents perfluoroalkyl of one carbon atom, R2-R5 each represent hydrogen, and R6 represents CH_2CH_2OR7, where R7 represents hydrogen), for examination on the merits in the reply filed May 8, 2009.

Applicant is required to affirm the presently elected subject matter in any submission filed in

response to the instant Office Action.

The claims corresponding to the elected subject matter are claims 13-18 and such claims are herein acted on the merits.

Objection to the Oath/Declaration

The declaration filed September 29, 2005, which contains reference to a prior foreign application (EP 03291024.2, filed April 25, 2003), is defective because the declaration has not been executed in accordance with 37 C.F.R. 1.66 or 1.68 by providing an appropriate signature for the named inventor(s). A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by serial number and filing date is required. See MPEP §§ 602.01 and 602.02.

Objection to the Claims

Claim 17 is objected to because the phrase "...wherein the medicament comprises as active ingredient from 0.2 mg..." is grammatically awkward. Applicant may wish to consider amending the claim to read ---wherein the medicament comprises as an active ingredient from 0.2 mg--- to overcome this objection, but is advised that the adoption of such a suggestion will not necessarily obviate any other objection and/or rejection set forth herein the instant office action.

Claim 18 is objected to because the phrase "...is administered at doses comprised between 0.1 mg/kg to 10 mg/kg" is grammatically awkward. Applicant may wish to consider amending the claim to read ---is administered at a dose ~~comprised~~ between 0.1 mg/kg to 10 mg/kg--- to overcome this objection, but is advised that the adoption of such a suggestion will not necessarily obviate any other objection and/or rejection set forth herein the instant office action.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired.

In the present instance, claim 1 recites the limitation that "A represents a straight or branched alkylene chain of from 2 to 6 carbon atoms separating the nitrogen atoms linked thereto by at least two carbon atoms". However, the phrase "A represents a straight or branched alkylene chain of from 2 to 6 carbon atoms" limits the alkylene chain to a length of 2-6 carbon atoms between the two nitrogen atoms, but the subsequent phrase "separating the nitrogen atoms linked thereto by at least two carbon atoms" is a broader recitation of the number of carbon atoms that may be contained within the alkylene chain (i.e., at least 2 or more carbon atoms). As a result, it is unclear which phrase is meant to limit the instantly claimed subject matter. Accordingly, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the scope of subject matter for which Applicant is presently seeking protection. Clarification is requested.

Moreover, instant claim 1 recites the broad limitation "lower alkyl-sulfonyl", but then recites "preferably methylsulfonyl", which is a narrower statement of the limitation. The phrase "preferably" renders the claim indefinite because it is unclear whether the limitation following the phrase is (a) merely exemplary of the remainder of the claim (i.e., that a type of "lower alkyl-sulfonyl" is methylsulfonyl, and therefore not required, or (b) a required feature of the claims (i.e., that the claims are intended to be

limited to methylsulfonyl only). Clarification is requested.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claims 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In particular, there is insufficient antecedent basis for the limitation "the medicament" in line 1 of each of claims 16-18, since the preceding text of the claims or those from which they depend fail to set forth any reference to "a medicament" *per se*.

For this reason, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunlop et al. ("Fluphenazine Dihydrochloride-An Anti-Anxiety Agent", *Journal of Neuropsychiatry*, 1962 Mar-Apr; 3:251-253) in view of Pongratz ("Treatment of Psychiatric Symptoms in Amyotrophic Lateral Sclerosis", *European Neuropsychopharmacology*, 2000; 10(Suppl.3):S116-117).

Dunlop teaches the administration of a new phenothiazine derivative, fluphenazine dihydrochloride, in the form of a sustained action tablet (also known as PERMITIL), to 71 ambulatory patients of varying age (col.2, para.4, p.251). Dunlop teaches that fluphenazine dihydrochloride is clinically effective in fractional milligram doses and exhibits a rapid onset of action that is capable of alleviating symptoms of anxiety without dulling alertness (col.1, para.2, p.251). Dunlop teaches that the sustained release tablet contains 1 mg fluphenazine dihydrochloride, half of which is in the outer coating and the other half contained in a barrier-protected inner core (col.2, para.2, p.251). Table I demonstrates that 66 of 71 patients demonstrated a good response to treatment with the disclosed fluphenazine dihydrochloride tablet (i.e., meets Applicant's limitation directed to the compound administered via the oral route as recited in instant claim 16), and 5 of 71 patients demonstrated a fair response to treatment with the same (col.1, p.252), wherein Dunlop further states that the most striking feature of the medication was the relief of anxiety in the absence of drowsiness (col.1, para.3, p.252). Still further, Dunlop discloses an additional study of fluphenazine dihydrochloride sustained-release tablets, where 10 patients were administered 2-4 mg/day and 9 of 10 patients demonstrated a favorable response and 1 of 10 patients demonstrated a fair response (col.2, para.2, p.252). Dunlop observed that these 10 patients received considerably in excess of the usual 1 mg single daily dose, but the patients did not experience the usual side effects seen with typical phenothiazine compounds (col.2, para.2, p.252).

Dunlop fails to specifically teach the treatment of amyotrophic lateral sclerosis in a patient in need of such treatment (claim 13) or that the fluphenazine dihydrochloride is administered at a dose between 0.1 mg/kg to 10 mg/kg (claim 18).

Pongratz teaches that amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that affects both central and peripheral motor neurons (col.2, para.1, p.S116). Pongratz teaches that ALS is characterized by progressive aggravation of motor deficit as a result of increasing loss of motor neurons and further teaches that the most important additional clinical features in advanced stages of ALS are, *inter alia*, psychiatric disturbances, such as anxiety and depression, and determines that anxiety in endstage ALS occurs is 32% of patients (col.2, Table 1, p.S116).

In view of such teachings, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention that the disclosed fluphenazine dihydrochloride formulation of Dunlop for the treatment of anxiety would have been reasonably expected to exert the same or substantially equivalent efficacy in the treatment of amyotrophic lateral sclerosis in a patient in need of such treatment because: (1) the composition of Dunlop was known to have efficacy in treating patients that suffer from anxiety *per se* (i.e., anxiety of any etiology) and (2) a significant proportion of patients (i.e., at least 32%, as evidenced by Pongratz) that have amyotrophic lateral sclerosis suffer from concomitant anxiety. Dunlop provides the clear teaching that the instantly claimed fluphenazine dihydrochloride is, in fact, effective for treating all anxiety patients, i.e., 100% of patients with anxiety, without exclusion. Of this entire population of anxiety patients, Pongratz provides the factual extrinsic evidence demonstrating that a subpopulation of anxiety patients also suffers concomitantly from amyotrophic lateral sclerosis. Accordingly, the suggestion of Dunlop to use the claimed fluphenazine dihydrochloride formulation for treating any anxiety patient is a clear suggestion to use it in any subpopulation of anxiety patients, such as those patients also suffering from concomitant amyotrophic lateral sclerosis, with the reasonable expectation of the same (or at least substantially equivalent) level of efficacy in treating this subpopulation of patients with amyotrophic lateral sclerosis as would be expected in the treatment of anxiety patients *per se*. Furthermore, since products of identical composition cannot have mutually exclusive properties when administered under identical conditions, or, as in the present case, the same

host, whatever effect(s) the instantly claimed fluphenazine dihydrochloride formulation has in treating amyotrophic lateral sclerosis must necessarily be present in the method disclosed by Dunlop, absent factual evidence to the contrary. See MPEP §2112.

Furthermore, regarding the administration of the fluphenazine compound at a dose of between 0.1 mg/kg and 10 mg/kg (claim 18), Dunlop clearly teaches that the disclosed fluphenazine dihydrochloride tablets were administered to subjects suffering from anxiety in amounts that were "considerably in excess" of the usual 1 mg single daily dose and were effective to achieve the treatment of anxiety without the usual adverse effects seen with other phenothiazine compounds (col.2, para.2, p.252). Accordingly, though Dunlop does not *per se* teach the use of fluphenazine dihydrochloride in an amount of, specifically, 0.1-10 mg/kg (claim 18), the determination of the optimal dosage amount would have been a matter well within the skill of the artisan at the time of the invention and would not have required undue experimentation or have been outside the realm of knowledge generally available to the skilled artisan. Factors that would have been taken into consideration when making such a determination would have included, but not been limited to, the age, weight, sex, diet and medical condition of the patient, severity of the disease, route of administration, pharmacological considerations, e.g., activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination, as well as the fact that higher doses of the disclosed fluphenazine composition were known to effect the treatment of anxiety in the absence of adverse effects. Thus, the dosage amount of fluphenazine dihydrochloride that would have actually been employed would have been expected to vary widely and, in the absence of evidence to the contrary, would not have been inconsistent with that which is presently claimed, particularly in view of the teachings of Dunlop that the disclosed fluphenazine composition can be administered in higher doses for the treatment of anxiety but without an increase in adverse effects seen with the medication.

Conclusion

Rejection of claims 13-18 is proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LESLIE A. ROYDS whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

June 18, 2009

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614